Original Article

Frequent Central Nervous System Failure After Clinical Benefit With Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Korean Patients With Nonsmall-Cell Lung Cancer

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BACKGROUND: We investigated the risk of central nervous system (CNS) failure after clinical benefit with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) in Korean patients with nonsmall-cell lung cancer (NSCLC) **METHODS:** We retrospectively evaluated the pattern of disease progression of 287 advanced NSCLC patients who were treated with gefitinib or erlotinib. Patients whose best tumor response was complete response, partial response, or stable disease (≥90 days) were classified into the group receiving clinical benefit with these drugs. **RESULTS:** The clinical benefit group had a higher incidence of CNS failure as an initial progression, compared with the non-clinical benefit group (26% vs 4%; $P < .001$). Isolated CNS failure was also more frequent in the clinical benefit group than in the non-clinical benefit group (13% vs 1%; $P < .001$). In a multivariate analysis, clinical benefit with EGFR-TKIs significantly increased the risk of isolated CNS failure, with an adjusted hazard ratio of 10.9 (95% confidence interval [CI], 1.4-29.1, $P = .01$). In patients with isolated CNS failure, the median time from initial intracranial failure to extracranial failure was 9.9 months (95% CI, 1.9-21.9 months) and to death was 12.9 months (95% CI, 3.3-22.5 months). **CONCLUSIONS:** The CNS was frequently the initial failure site after clinical benefit with EGFR-TKIs in Korean NSCLC patients. Patients with isolated CNS failure showed durable extracranial control after cranial progression. A role for close surveillance of the CNS during EGFR-TKI treatment or prophylactic measures appears worthy of further study in these patients. ***Cancer* 2010;116:1336–43.** © *2010 American Cancer Society.*

KEYWORDS: nonsmall cell lung cancer, epidermal growth factor receptor, central nervous system, recurrence, brain-blood-barrier.

In recent years, many targeted agents have been developed to improve the typically dismal outcome associated with nonsmall-cell lung cancer (NSCLC). In particular, a small molecule drug inhibiting the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) is the first targeted agent to be successfully used in practice in advanced NSCLC. In several prospective studies, these EGFR tyrosine kinase inhibitors (EGFR-TKIs) showed modest tumor shrinkage rates of 9%-26%.[1-3] However, in a phase 3 trial with previously treated advanced NSCLC, EGFR-TKIs provided a survival benefit over best supportive care, with a hazard ratio of 0.70.[4] In addition, several highly predictive clinical or biological factors for response to EGFR-TKIs have been identified; these include female gender, never smoking, East Asian descent, adenocarcinoma histologic type, and *EGFR* mutations.[5-7] However, patterns of progression or long-term outcomes after an initial response to EGFR-TKIs have not yet been fully investigated.

Central nervous system (CNS) metastasis is a prevalent and serious complication, with negative effects on quality of life and overall survival.[8-10] In particular, it has been known to develop more frequently in patients with younger age, female gender, adenocarcinoma histology, or late-stage presentation.[11-14] Recently, there has been a refocus on CNS

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metastasis as peripheral tumor control further improved. For example, CNS relapse is a major problem in managing locally advanced NSCLC, in which aggressive trimodal treatment has enhanced primary tumor control and improved overall survival.[15,16] In addition, frequent CNS metastases have been anecdotally reported in advanced NSCLC patients showing durable responses to targeted therapy such as EGFR-TKIs. Omuro et al reported that the incidence of the CNS as an initial failure site reached 33% in EGFR-TKI responders with advanced NSCLC.[17] A similar phenomenon has been previously observed in other types of tumor, such as human epidermal growth factor receptor 2 (HER2)-overexpressing metastatic breast cancer (MBC) achieving prolonged survival with trastuzumab-based treatment.[18,19]

A high incidence of CNS progression after a response to EGFR-TKIs may be more important in an Asian NSCLC population, because EGFR-TKI therapy has been shown to be more effective in this ethnic group.[1,2] However, there are no published data on the incidence of CNS progression after a response to EGFR-TKIs in Asian patients. Thus, we evaluated the pattern of disease progression in Korean NSCLC patients who used EGFR-TKIs, focusing on the incidence, characteristics, and risk factors for CNS metastasis.

MATERIALS AND METHODS

Patients

We reviewed 342 patients who were diagnosed with histologically confirmed recurrent or metastatic NSCLC and who were subsequently treated with either gefitinib or erlotinib at Yonsei University College of Medicine (Seoul, Korea) between January 2002 and January 2008. We excluded patients who had stopped drug treatment within 1 month, for any reason. Patients with CNS metastasis were included if they had received local treatment, such as whole-brain radiotherapy (WBRT), radiosurgery, or other surgery, and their CNS status was thereafter clinically and radiologically stable before EGFR-TKI treatment. As a result, 287 eligible patients were enrolled in the final cohort.

The institutional review board approved this study. As the study was a retrospective analysis, the institutional review board waived informed consent requirements.

Treatment and Evaluation

Patients received daily treatment with gefitinib (250 mg/d) or erlotinib (150 mg/d). Tumor response was evaluated by computed tomography (CT) every 8 weeks, in accordance with the guidelines established by the Response Evaluation Criteria in Solid Tumor (RECIST) committee.[20] To evaluate neurological symptoms and to detect any change in pre-existing CNS disease, magnetic resonance imaging (MRI) or CT was performed. On detection of CNS progression, extracranial sites were also fully re-evaluated.

Biomarker Analysis

Nucleotide sequencing of the EGFR kinase domain (exons 18-21) was performed using nested polymerase chain reaction (PCR) amplification of individual exons. Details of the sequencing procedure have been described elsewhere.[21] Mutations in K-*RAS* codons 12 and 13 were identified as previously described.[22]

Statistical Analysis

CNS metastasis includes all cases of parenchymal metastasis and cytologically or radiologically proven leptomeningeal carcinomatosis. CNS failure means both newly developed metastasis and progression of pre-existing lesions. Patients whose best tumor responses were complete response, partial response (PR), or stable disease (SD) for more than 90 days were classified into the group that received clinical benefit with EGFR-TKIs.

Time from diagnosis to progression was measured from the diagnosis of recurrent or metastatic disease until progression occurred after EGFR-TKI therapy. Time to progression (TTP) or overall survival (OS) was defined as the period from the initiation date of EGFR-TKI therapy to the date of progression or death, respectively. Survival time was estimated by the Kaplan-Meier method, and the survival difference between groups was assessed by the log-rank test. Fisher exact test was used to compare the frequency of CNS failure according to the risk factors. To calculate the actuarial incidence of CNS failure by the Kaplan-Meier method, patients were censored after recurrence at other sites or after death from other causes. To assess the strength of interaction between risk factors and CNS failure, logistic regression analysis was used. All statistical tests were 2-sided, with the level of significance set at 0.05.

RESULTS

Patient Characteristics

Baseline patient characteristics are shown in Table 1. The median age was 60 years (range, 30-88 years). Among 145

Table 1. Patient Characteristics

Characteristics	Clinical Benefit,[a] n=166	Non-Clinical Benefit, n=121	*P*[b]
Age, y			NS
<65	101 (61%)	82 (68%)	
≥65	65 (39%)	39 (32%)	
Sex			NS
Men	76 (46%)	68 (56%)	
Women	90 (54%)	53 (44%)	
ECOG			.001
0 or 1	124 (75%)	65 (54%)	
2 or 3	42 (25%)	56 (46%)	
History of smoking			<.001
Never	106 (64%)	39 (32%)	
Ever	60 (36%)	82 (68%)	
Histology cell type			.05
Adenocarcinoma	123 (74%)	76 (63%)	
Squamous cell carcinoma	23 (14%)	25 (21%)	
Others	20 (12%)	20 (17%)	
Stage[c]			NS
IIIB	5 (3%)	4 (3%)	
IV	161(97%)	117 (97%)	
***EGFR* mutations**			<.001
Yes	43 (26%)	5 (4%)	
No	49 (30%)	48 (40%)	
Unknown	74 (44%)	68 (56%)	
***K-RAS* mutations**			.007
Yes	0 (0%)	6 (5%)	
No	88 (53%)	45 (37%)	
Unknown	78 (47%)	70 (58%)	
EGFR-TKI type			NS
Gefitinib	124 (75%)	82 (68%)	
Erlotinib	42 (25%)	39 (32%)	
No. of previous chemotherapy			NS
<3	153 (92%)	110 (91%)	
≥3	13 (8%)	11 (9%)	
Previous CNS metastasis			NS
Yes	15 (10%)	14 (12%)	
No	151 (90%)	107 (88%)	

NS indicates not significant; ECOG, Eastern Cooperative Group; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; CNS, central nervous system; WBRT, whole-brain radiotherapy.
[a] Patients with a clinical benefit to epidermal growth factor receptor tyrosine kinase inhibitor.
[b] Frequency, tested by $\chi 2$ test.
[c] Staging according to the revised International System for Staging Lung Cancer.

patients subjected to *EGFR* mutation analysis, 48 (33%) patients showed exon 19 deletion or L858R point mutations. Twenty-nine (10%) patients had pre-existing CNS metastasis before EGFR-TKI therapy; their treatments for previous CNS metastasis included WBRT alone (n = 16), radiosurgery (n = 10), and other surgery (n = 3). Significant differences between the clinical benefit and non-clinical benefit groups were seen for smoking history, performance status, histologic type, *EGFR* mutation, and *K-RAS* mutations.

Treatment Outcomes

On October 1, 2008, the median follow-up times for total patients and survivors were 13.2 months (95% confidence interval [CI], 12.0-18.4 months) and 21.4 months (95% CI, 21.0-25.8 months), respectively. Among total

Table 2. Pattern of Failure

Progression Site	Clinical Benefit[a] (n=127)	Nonclinical Benefit (n=105)	Total (n=232)
	No. (%)	No. (%)	No. (%)
Lung	75 (59)	71 (68)	146 (63)
Any CNS	33 (26)	4 (4)	37 (16)
CNS only	16 (13)	1 (1)	17 (7)
CNS plus other sites	17 (13)	3 (3)	20 (9)
Others	19 (15)	30 (28)	49 (21)

CNS indicates central nervous system.
[a] Patients with a clinical benefit to epidermal growth factor receptor tyrosine kinase inhibitor.

patients, the median TTP and OS were 3.9 months (95% CI, 3.2-4.6 months) and 13.6 months (95% CI, 11.4-15.7 months), respectively. The best tumor responses included PR (n = 82, 29%), South Dakota ≥90 days (n = 81, 28%), South Dakota <90 days (n = 9, 3%), and progressive disease (PD; n = 115, 40%). The clinical benefit group (n = 163, 57%) was significantly associated with longer TTP (8.5 vs 1.7 months; $P < .001$), longer time from diagnosis to progression (19.4 vs 10.6 months; $P < .001$), and longer OS (24.5 vs 4.3 months; $P < .001$) than the non-clinical benefit group.

Pattern of Failure

In the analysis of the 232 evaluable patients, the site of first failure was lung in 146 (63%) patients, CNS in 37 (16%), and other sites in 49 (21%; Table 2). The clinical benefit group had a higher incidence of CNS failure as the first failure site, compared with the non-clinical benefit group (26% vs 4%; $P < .001$). Moreover, isolated CNS failure, without other systemic progression, was more frequent in the clinical benefit group than in the non-clinical benefit group (13% vs 1%; $P < .001$). In an analysis limited to newly developed CNS metastasis, the difference in the rate of isolated CNS failure between the 2 groups remained significant (11% vs 1%; $P = .02$). In the clinical benefit group, the actuarial 1-year and 2-year rates for isolated CNS failure were 14 and 37%, respectively (Fig. 1).

Risk Factors for Isolated CNS Failure

In the univariate analysis, never smokers, patients with adenocarcinoma, the clinical benefit group, and those with a longer time from diagnosis to progression had significantly higher risk for isolated CNS failure (Table 3). However, in the multivariate analysis, only clinical benefit from EGFR-TKIs was an independent predictor of isolated CNS failure, with an adjusted hazard ratio (HR) of 10.9 (95% CI, 1.4-29.1, $P = .01$).

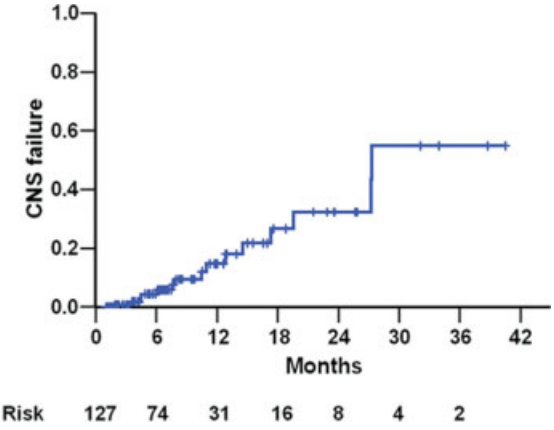

Figure 1. The actuarial incidence of isolated central nervous system failure, measured by the Kaplan-Meier method, in patients with clinical benefit from epidermal growth factor tyrosine kinase inhibitors.

In a subset analysis, a strong association between clinical benefit from EGFR-TKIs and isolated CNS failure was still observed for never smokers (adjusted HR of the clinical benefit vs non-clinical benefit group, 10.7; 95% CI, 1.3-26.7; $P = .02$) and for patients with adenocarcinoma (adjusted HR, 11.6; 95% CI, 1.4-21.6; $P = .02$), but not for patients with a median time from diagnosis to progression of more than 12 months (adjusted HR, 4.27; 95% CI, 0.5-34.9; $P = .17$).

Characteristics of Isolated CNS Failure

The characteristics of 17 patients experiencing isolated CNS failure after treatment with EGFR-TKIs are presented in Table 4. Of the 4 patients with pre-existing CNS metastasis, 2 patients with single brain metastasis had been managed with radiosurgery alone, and 2 patients with several brain metastases had been treated with WBRT. Most of the patients with isolated CNS failure had clinical benefit from EGFR-TKIs (n = 16; 94%). After EGFR-TKI failure, 12 (71%) patients subsequently received chemotherapy, including 10 (59%) patients who continued on EGFR-TKIs and 2 (12%) patients who were treated with pemetrexed (Alimta). The median time from initial intracranial failure to extracranial failure was 9.9 months (95% CI, 1.9-21.9 months). Patients with isolated CNS failure had a longer median time from initial failure to death, compared with those with other site failures (12.9 months; 95% CI, 3.3-22.5 months) versus 6.0 months (95% CI, 4.5-7.5 months; $P = .01$; Fig. 2).

Table 3. The Risk Factors of Isolated CNS Failure

Variables (Reference Group)	Univariate[a]		Multivariate[a]	
	HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Age (≥65 years)	2.4 (0.7-8.4)	.19	—	—
Gender (male)	2.5 (0.8-7.2)	.10	—	—
Smoking (smoker)	3.7 (1.0-13.7)	.05	1.7 (0.4-6.7)	.42
Histology (nonadenocarcinoma)	8.4 (1.1-18.1)	.04	6.5 (0.8-51.8)	.08
EGFR (wild type)	2.8 (0.8-10.3)	.10	—	—
Previous CNS metastasis (absence)	2.1 (0.7-5.8)	.14	—	—
Previous chemotherapy (<3)	1.7 (0.2-13.7)	.60	—	—
Clinical benefit to EGFR-TKIs (non-clinical benefit[b])	15.8 (1.4-9.1)	.001	10.9 (1.4-29.1)	.01
Time from diagnosis to isolated CNS failure[c]	1.04 (1.0-1.1)	.008	1.01 (0.9-1.1)	.47

CNS indicates central nervous system; HR, hazard ratio; CI, confidence interval; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.
[a] By the logistic regression analysis.
[b] Patients without a clinical benefit to epidermal growth factor receptor tyrosine kinase inhibitor.
[c] Used as continuous value.

Table 4. The Characteristics of Isolated CNS Failure

Characteristics	No.	%
Previous CNS metastasis	4	24
Neurological symptoms at diagnosis	12	71
Leptomeningeal carcinomatosis	3	18
Multiple metastases	14	82
Local treatment for CNS metastasis		
WBRT alone	6	35
Radiosurgery ± WBRT	4	24
Operation ± WBRT	4	24
None	3	18
Chemotherapy after isolated CNS failure		
EGFR-TKIs	10	59
Pemetrexed	2	12
None	5	29

CNS indicates central nervous system; WBRT, whole-brain radiotherapy; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor.

Subsequent Systemic Therapy After Isolated CNS Failure

Ten patients continued EGFR-TKIs after CNS failure. The median age of these patients was 54 years (range, 35-71 years); all were female and never smokers, and 9 of them had adenocarcinoma-type histology. *EGFR* gene mutation analysis was conducted in 6 of the 10 patients; 3 (50%) harbored activating mutations in the *EGFR* gene. Best tumor responses to the first EGFR-TKIs were PR in 3 patients and SD in 7. The median first TTP was 10.9 months (95% CI, 8.9-26.5 months), and the median second TTP was 10.0 months (95% CI, 1.9-20.4 months). The median time from initial failure to death was 14.0 months (95% CI, 2.1-27.8 months).

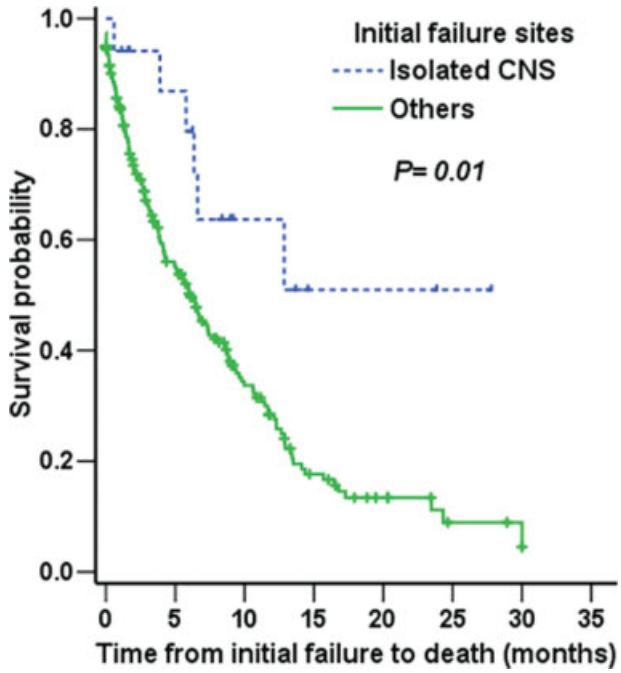

Figure 2. The Kaplan-Meier survival curves for time from initial failure to death according to initial failure site, in advanced nonsmall-cell lung cancer patients treated with epidermal growth factor tyrosine kinase inhibitors.

DISCUSSION

To our knowledge, this is the first report on the incidence of CNS failure after EGFR-TKI therapy in an Asian NSCLC cohort. A comprehensive analysis of 287 patients revealed that 26% of the patients with clinical benefit from EGFR-TKIs experienced CNS failure as the first

progression. This rate is consistent with a previous report by Omuro et al[17] Multivariate analysis confirmed that a clinically beneficial response to the drugs was an independent risk factor for isolated CNS failure. Moreover, when the analysis was limited to patients with adenocarcinoma, a well-known risk factor for CNS metastasis in NSCLC,[13] the relationship between clinical benefit from EGFR-TKIs and isolated CNS failure remained significant. Nevertheless, the present study has intrinsic weaknesses as a retrospective study. In particular, the incidence of CNS metastasis might have been underestimated, because complete restaging was not performed at disease progression in some patients. Thus, a prospective study with restaging will be needed to validate the frequent CNS failure in a group receiving clinical benefit with EGFR-TKIs.

The mechanism underlying the relationship between clinical benefit from EGFR-TKIs and CNS metastasis remains to be determined. Several causal factors may be involved. First, prolonged survival through the use of EGFR-TKIs may coincide with a substantial risk for developing CNS metastasis, as the cranial event occurs in a relatively late phase of the disease. The group with clinical benefit from EGFR-TKIs survived significantly longer from the initial diagnosis to the first failure after EGFR-TKI therapy. In the analysis of subjects with a median time from diagnosis to progression of more than 12 months, no difference was observed in the rate of isolated CNS failure between the groups with and without a clinical benefit from EGFR-TKIs. However, because the multivariate test eventually confirmed that a clinically beneficial response to the drugs, but not prolonged survival, was a risk factor for isolated CNS failure, prolonged survival alone cannot explain the prevalence of CNS metastasis. Second, tumors that are sensitive to EGFR-TKIs may have a high intrinsic potential for CNS metastasis. Somatic *EGFR* mutations are the most dominant predictor of a clinical response to EGFR-TKIs.[5-7] In a recent report, Matsumoto et al proposed that the high frequency of *EGFR* mutations in brain metastases of lung adenocarcinoma suggests an intrinsic brain tropism of these tumors.[23] The present study confirmed that tumors harboring *EGFR* mutations tended to be associated with a greater risk for isolated CNS failure, compared with tumors having wild-type *EGFR*. On the other hand, Huang et al reported that the overexpression of STAT3, an important mediator of the oncogenic effects of *EGFR* mutations,[24] was strongly associated with brain metastasis in human melanoma cells.[25] Further studies are required to determine whether *EGFR* mutations endow tumor cells with metastatic propensity to the CNS. Third, incomplete drug penetration of the brain-blood barrier may account for the increased incidence of CNS metastasis. Those patients showing isolated CNS failure developed CNS recurrence or progression despite apparently excellent extracranial control. These results may indicate that drug delivery to the CNS was hindered, thus permitting CNS failure. In a preclinical study in nontumor-bearing rats, radiolabeled (^{14}C)-gefitinib showed very limited distribution in the CNS.[26] In a case report of NSCLC with leptomeningeal carcinomatosis treated with gefitinib, Jackman et al showed that cerebrospinal fluid drug levels were below the level required for tumor growth inhibition, even at a gefitinib dose of 500 mg/d.[27] However, because a number of clinical studies have reported the successful treatment of CNS metastasis with standard or high doses of EGFR-TKIs,[28-30] we cannot presently reach any conclusion regarding the impermeability of the brain-blood barrier to EGFR-TKIs. Additional studies to collect pharmacokinetic data for small, targeted molecules or to determine predictors for the brain-blood barrier breakdown would be useful. Fourth, metastatic CNS clones may possess an inherited resistance to EGFR-TKIs, or they may acquire earlier drug resistance during EGFR-TKI therapy. For example, a small study analyzing the second *EGFR* mutation in patients who showed progression after EGFR-TKI therapy revealed that the type and nature of acquired resistance in EGFR mutants may differ between the CNS and the periphery.[31] Thus, both intrinsic characteristics of metastatic cells and the unique microenvironment of the CNS may contribute to differing patterns of resistance.

Understanding these mechanisms may aid in determining treatment strategies beyond progression in patients with isolated CNS failure. However, the current data are insufficient to answer the question as to whether we should continue EGFR–TKI treatment even after progression in this population. In several retrospective studies in HER2+ MBC, the continuation of trastuzumab beyond brain metastasis prolonged post-PD survival, owing to a sustained antitumor activity at extracranial and/or intracranial sites.[32-34] In addition, there is increasing interest in the benefit of a second EGFR-TKI after failure of a first EGFR-TKI in advanced NSCLC, regardless of the failure site.[35,36] We previously reported that erlotinib, as a salvage treatment, achieved a 28.6% disease control rate and a 9.5% response rate in patients who failed with gefitinib.[37] Thus, a randomized study to

extend EGFR pathway blockade after first progression is warranted in patients harboring a potential to maintain the efficacy of EGFR-TKIs with acceptable toxicity.

In the present study, the majority of patients who experienced isolated CNS failure showed durable extracranial control even after cranial progression. These results suggest that prophylactic measures or early detection and radical treatment of CNS metastasis may help to prolong the response duration of EGFR-TKIs and to reduce cranial complications in selected populations. In locally advanced NSCLC, with a 15%-30% CNS relapse risk,[14,15] several studies have already reported that prophylactic cranial irradiation significantly reduced the CNS relapse rate, by 5%-10%,[38-41] and a prospective study to examine the survival benefit of prophylactic cranial irradiation is currently underway. On the basis of these results, we have proposed a randomized phase 3 trial addressing the efficacy and toxicity of prophylactic cranial irradiation in patients with advanced NSCLC who are nonprogressive on gefitinib or erlotinib.

In conclusion, this study shows that the CNS is a frequent site of initial failure in Korean patients with advanced NSCLC who had a clinically beneficial response to EGFR-TKI therapy. Additional large, prospective studies to determine an accurate rate of CNS metastasis and preclinical studies on drug resistance mechanisms are required to better understand this phenomenon.

CONFLICT OF INTEREST DISCLOSURES

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